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Effect of increased plasma osmolality on cold-induced thirst attenuation

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Abstract The effects of elevating plasma osmolality (P_{osm}) on thirst ratings was studied in eight dehydrated males during exposure to 4°C. On two occasions, subjects were dehydrated (DH; 3–4% body mass) via 90 min exercise-heat exposure and overnight fluid restriction (day 1). On a third occasion, subjects were exposed to heat but were given fluid (EU). On day 2, subjects consumed NaCl (NaCl; 0.1 g NaCl kg⁻¹ body mass in 500 ml H₂O; DH only) or Placebo (P; 500 ml H₂O; DH and EU). Subjects stood for 30 min at 24°C and for 45 min at 4°C (75 min post-dose). P_{osm} was elevated ($P < 0.05$) 30 and 75 min after NaCl administration in DH + NaCl versus DH + P and EU + P treatments. Thirst ratings remained elevated ($P < 0.05$) in the DH + NaCl treatment 30 min after dosing and 45 min at 4°C versus DH + P and EU + P. Attenuation of thirst when dehydrated in the cold can be over-ridden by increasing P_{osm} .

Keywords Dehydration · Thirst · NaCl load · Cold exposure

Introduction

Two primary mechanisms exist in order to maintain body fluid balance; one mechanism regulates renal water retention and loss, whereas the second stimulates thirst resulting

in voluntary fluid intake. Oropharyngeal and gastric stimuli, as well as blood volume and plasma osmolality (P_{osm}) are important factors modifying thirst (Greenleaf 1992). Stimuli affecting circulating volume (dehydration, hemorrhage) or P_{osm} (hypotonic sweat loss) will induce drinking with each factor acting individually or in combination (Greenleaf 1982). Under most circumstances fluid consumption in humans is precipitated by sweat and urine fluid losses. This type of dehydration leads to a simultaneous elevation in P_{osm} and decrease in plasma volume resulting in the stimulation of thirst.

The threshold for the stimulation of thirst at rest in humans is proposed to occur at approximately 0.8% body mass loss (Wolf 1950) or at a P_{osm} of ~290 mOsm kg⁻¹ of H₂O (Phillips et al. 1985). However, the osmotic threshold for thirst has been shown to be altered by independent changes in central volume. A decrease in thirst sensations has been reported in hyperosmotic subjects when their central volume was expanded via head-out water immersion (Wada et al. 1995). Further studies have also reported a decrease in thirst sensations as well as fluid intake during head-out immersion and concluded that central volume expansion exerted an inhibitory influence on thirst and drinking behavior (Sagawa et al. 1992; Stachenfeld et al. 1997). Although central volume may be elevated by head-out water immersion, other stimuli also have a similar effect. In resting dogs exposure to cold temperatures has been reported to result in an increase in the osmotic threshold for the stimulation of thirst due to an increase in central blood volume (Sobocinska and Kozlowski 1987).

Recently, we reported (Kenefick et al. 2004a) a decrease (up to 40%) in arginine vasopressin release and thirst sensations in eu- and dehydrated men (−4% body mass), both at rest and during exercise, when exposed to 4°C air. Similar to Sobocinska and Kozlowski (1987), we hypothesized that

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this thirst response to cold exposure in humans was likely due to an increase in central volume, secondary to cold-induced peripheral vasoconstriction. No study has yet determined if the osmotic threshold for thirst is altered in individuals exposed to a cold environment. On an acute basis, dehydration in the cold may be less of a concern regarding health or exercise performance compared to a warmer environment. However, chronic dehydration has been noted as a major problem for individuals during long term exposure to cold and could possibly increase the risk of peripheral cold injury (O'Brien et al. 1998). Thus the purpose of the present study was to determine whether elevating P_{osm} of already hyperosmotic subjects exposed to cold would overcome the inhibitory effect of cold on thirst. We hypothesized that by increasing P_{osm} beyond the elevated osmotic threshold for thirst due to cold exposure, the sensation of thirst would be restored.

Methods

Subjects

Eight men who were not heat or cold acclimated volunteered to participate in this study. Their physical characteristics were (mean \pm SD): age, 24.1 ± 5.5 year; height, 179.6 ± 10.5 cm; body mass, 78.0 ± 13.4 kg; $\text{VO}_{2\text{max}}$, 56.1 ± 5.9 ml $\text{kg}^{-1} \text{min}^{-1}$; and percent body fat, $9.9 \pm 2.4\%$. Before participation, each subject completed a written informed consent document and a medical history questionnaire after being informed of the purpose of the experiment and possible risks. This study protocol was approved in advance by the Committee on the Use of Human Subjects in Research at the University. Subjects were not paid for their participation.

Preliminary measures

Body mass was determined for each subject using an electronic scale (General GE510, Cape Coral, FL), followed by measures of maximal oxygen consumption ($\text{VO}_{2\text{max}}$, ml $\text{kg}^{-1} \text{min}^{-1}$) via a modified Costill-Fox treadmill test (Costill and Fox 1969). Body density was estimated using skinfold calipers (Harpندن, Ann Arbor, MI, USA) and procedures and equations as described by Jackson and Pollock (1978). Percent body fat was then calculated using the Siri equation (Siri 1993).

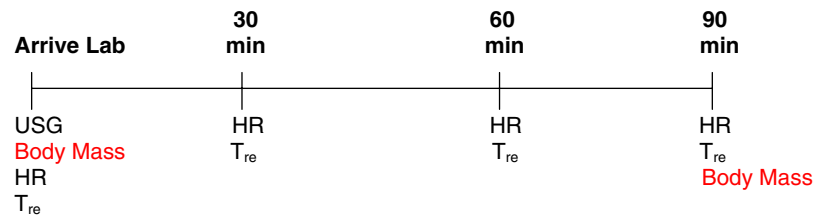
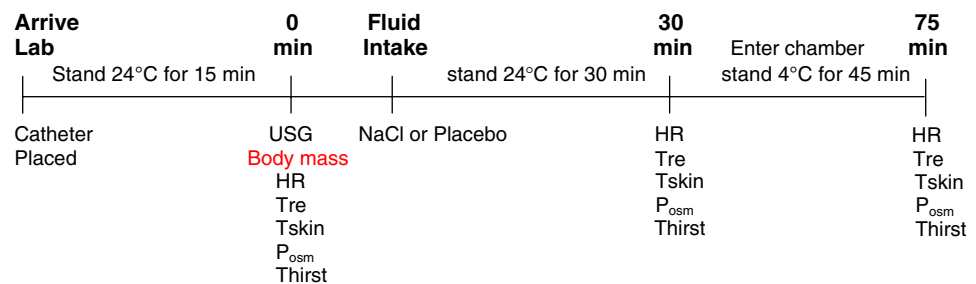
Experimental design

Following preliminary measures, each subject underwent 3 experimental treatments, performed at random, 1 week

apart. The three trials differed in pretest hydration state [euhydrated (EU) or dehydration (DH)], and in whether subjects ingested a sodium supplement (NaCl) or a placebo supplement (P). For the purpose of clarity, the term dehydration will be used throughout the manuscript and will be defined as a body water deficit. On day 1 of experimentation, subjects exercised in the heat with (EU) or without (DH) fluid replacement. Subjects were weighed before and after exercise to ensure a maintenance or loss ($\sim 4\%$) of body mass, respectively. Subjects were then instructed to eat and drink as normal (EU) or to refrain from fluid consumption and eat relatively dry meals to ensure that dehydration was maintained overnight (DH). On the morning of day 2, subjects consumed a sodium chloride drink (DH + NaCl) or a placebo drink (DH + P) when DH. When in the EU state, subjects consumed the placebo drink only (EU + P). After consuming the NaCl or P drinks, subjects stood for 30 min at room temperature (24°C , 50% rh) and then entered an environmental chamber set to 4°C , 50% rh and stood for an additional 45 min. For all three trials, subjects started day 1 and day 2 protocols at the same time of day and wore similar clothing (i.e. t-shirt, shorts, socks, and shoes). Day 1 and 2 protocols are presented in Fig. 1.

Dehydration protocol (day 1)

All dehydration sessions were conducted on the afternoon ~ 9.5 h before the start of the experimental sessions the next morning. This was done to reduce the potential for acute or residual heat exposure to affect thirst ratings (Kenefick et al. 2006). Subjects reported to the laboratory on the afternoon of day 1. A urine specific gravity (USG; Spartan Refractometer, model A 300 CL, Japan) of less than 1.020 (Armstrong et al. 1998) was used to verify that subjects were adequately hydrated prior to dehydration. A Polar monitor (Polar Accurex II, Polar Instruments) was attached to each subjects chest for heart rate (HR) and a flexible rectal probe (Yellow Springs Instruments, series 401, Yellow Springs, OH, USA) was inserted ~ 10 cm past the anal sphincter to monitor core temperature (T_{re}). Heart rate and rectal temperature were monitored continually for safety during the dehydration protocol. The subjects then walked for 90 min in a hot environment ($37.1 \pm 0.4^{\circ}\text{C}$, $51.2 \pm 5.2\%$ RH) at $\sim 56.0 \pm 1.6\%$ $\text{VO}_{2\text{max}}$ in an environmental chamber (Harris Environmental Systems, Andover, MA, USA) to elicit exercise-induced dehydration. Absolute workloads differed between subjects, but were held constant within subjects from trial to trial. Two fans, directed at the subjects, were used to create airflow (2.3 m s^{-1}) and increase sweat evaporation. Body mass taken before and after exercise was used to determine the percent of dehydration achieved. Subjects were instructed to refrain from consuming fluids or wet foods overnight during both DH

Fig. 1 Experimental study design, day 1 and 2 protocols**Day 1; Afternoon****Day 2; Morning**

sessions. During the EU trials, subjects were encouraged to drink fluid ad libitum to maintain hydration.

Experimental testing (day 2)

On the morning of day 2, subjects reported to the laboratory between 05:00 and 09:00 and hydration status was verified by measurement of body mass, USG and later confirmed by P_{osc} . A 20 gauge Teflon catheter was then inserted into the ante-cubital vein of the right arm of each subject and a male luer adapter (model 5877, Abbott Hospital, Inc., Chicago, IL, USA) was inserted into the catheter port for acquisition of subsequent blood samples. The catheter port and male luer adapter were kept patent with heparin lock flush solution. Subjects were then fitted with a heart rate monitor, flexible thermistor for T_{re} , and skin thermistors (Yellow Springs Instruments, series 401, Yellow Springs, Ohio) at the following sites: chest, triceps, thigh, and calf, for determination of mean skin temperature (T_{sk}) (Ramanathan 1964). Baseline measures (time zero) (Fig. 1) were taken after 15 min of standing at room temperature to establish equilibrium. Subjects were then provided a bagel as well as 500 mL of water containing either placebo (Grape Kool-Aid) or NaCl (in Grape Kool-Aid) at a dosage of 0.1 g kg^{-1} of body mass (0 min). After dosing, subjects stood for 30 min at 24°C to allow for gastric emptying (30 min). Subjects then entered the environmental chamber set at 4°C , 60% rh and stood in the chamber for 45 min (75 min). A wind speed of 2.3 m s^{-1} generated by two fans was directed at subjects from a distance of $\sim 1 \text{ m}$.

During experimental trials HR, skin temperatures, T_{re} , and perceived thirst were recorded at baseline (immediately

prior to dosing; 0 min), after 30 min of standing at 24°C (30 min), and again after standing at 4°C for 45 min (75 min; Fig. 1). The thirst sensation scale is a numerical scale from 1 to 9 with associated word anchors (1 = not thirsty, 3 = a little thirsty, 5 = moderately thirsty, 7 = very thirsty, 9 = very, very thirsty) and has been shown to be valid and reliable (Engell et al. 1987). Although the act of drinking can decrease thirst transiently due to stimulation of oropharyngeal receptors in the mouth (Salata et al. 1987), thirst ratings at 75 min allowed sufficient time for any thirst depression due to oropharyngeal stimulus to subside (Salata et al. 1987) and allowed equilibration of the NaCl dose. Approximately 5 ml of whole blood was drawn at the same time points and was transferred to lithium heparin coated blood collection tubes (BD vacutainer). Blood was spun for 10 min at 9,500 g in a centrifuge. Plasma was drawn off for determination of P_{osc} . Fifty microliter aliquots of plasma were used in triplicate for measurement of P_{osc} (mOsm kg^{-1} of H_2O) by freezing point depression on a micro-osmometer (model Osmette, Precision Systems, Natick, MA, USA).

Statistical analysis

A general linear model (trial \times time) repeated measures analysis of variance was used to compare differences among treatments. F -values were adjusted accordingly (Atkinson 2001) where the assumption of sphericity was not met. Tukey's HSD procedure was used to identify differences among means following significant main and/or interaction effects. From Tran (1977), we interpolated that six to seven subjects would provide sufficient statistical

power ($\beta = 0.20$) to detect a difference in thirst rating equal to twice (1.0) the typical within-subjects standard deviation (0.5). The variability of thirst ratings was calculated from pilot data on eight subjects who rated thirst at rest on four separate occasions after being dehydrated by 3–4% of body weight. A difference of 1.0 on the thirst Likert scale (1–9) is $\sim 10\%$ and was considered meaningful. All data are reported as mean \pm SD. Statistical significance was accepted at $P < 0.05$.

Results

Each subject completed all three experimental trials. All volunteers were euhydrated prior to the start of the day 1 dehydration protocol as determined by urine specific gravity < 1.02 and $P_{\text{osm}} < 290 \text{ mOsm kg}^{-1}$ (Armstrong et al. 1998) (Table 1). Changes in body mass, urine specific gravity, and P_{osm} resulting from the day 1 dehydration protocol are presented in Table 1.

Plasma osmolality and perceived thirst

On the morning of day 2, dehydration in the DH + NaCl and DH + P was quantified by a 3.5–4% reduction in body mass, a urine specific gravity of ~ 1.026 , and P_{osm} of $\sim 295 \text{ mOsm kg}^{-1}$ of H_2O . Prior to any treatment, first morning thirst ratings were elevated ($P < 0.05$) in the DH + NaCl and DH + P trials compared to the EU + P trial (Table 1).

Physiological measures

There were no differences in T_{re} among the three treatments at any corresponding time point. T_{sk} was lower ($P < 0.05$) following exposure to 4°C at 75 min compared to 0 and 30 min, in all three treatments. Heart rate was lower ($P < 0.05$) at baseline (0 min) and 30 min after equilibration in the EU + P treatment compared to the DH + NaCl

Table 2 T_{re} , T_{sk} , and heart rate during experimental testing

	DH + NaCl	DH + P	EU + P
T_{re} ($^\circ\text{C}$)			
0 min	37.1 ± 0.3	36.8 ± 0.3	36.8 ± 0.3
30 min	37.1 ± 0.3	37.0 ± 0.3	36.8 ± 0.3
75 min	37.2 ± 0.4	37.1 ± 0.4	37.0 ± 0.3
Mean weighted T_{sk} ($^\circ\text{C}$)			
0 min	31.1 ± 0.9	31.5 ± 0.9	31.1 ± 0.4
30 min	30.9 ± 1.0	31.5 ± 1.0	31.0 ± 0.7
75 min	$21.1 \pm 0.8^*$	$20.5 \pm 0.8^*$	$20.4 \pm 0.8^*$
Heart rate			
0 min	81 ± 5	81 ± 10	$72 \pm 6^\#$
30 min	82 ± 13	82 ± 14	$73 \pm 8^\#$
75 min	82 ± 14	77 ± 13	71 ± 11

All data are presented as mean \pm SD

* Significant ($P < 0.05$) difference from baseline and 30 min value within a treatment

$^\#$ Significant ($P < 0.05$) difference from DH + NaCl and DH + P treatments

and DH + P treatments but was not different ($P < 0.05$) after exposure to 4°C (Table 2).

Within the DH + NaCl treatment, P_{osm} significantly increased ($P < 0.05$) from 0 to 30 min and from 30 to 75 min. There were no within-condition differences ($P > 0.05$) in the DH + P and EU + P treatments. Among treatments, P_{osm} was greater ($P < 0.05$) at minute 0, 30 and 75 min in both of the DH treatments compared to EU + P. P_{osm} was greater ($P < 0.05$) in the DH + NaCl versus DH + P treatment at 30 and 75 min (Fig. 2a).

Within the DH + NaCl treatment, ratings of thirst did decrease from 0 to 30 min but this decline was not significant ($P < 0.05$). From 30 to 75 min within the DH + NaCl treatment, thirst ratings increased ($P < 0.05$). Within the DH + P treatment, ratings of thirst declined ($P < 0.05$) from 0 to 30 min and from 30 to 75 min. Thirst ratings within the EU + P treatment were not different ($P > 0.05$) over the entire 75 min of observation. Among treatments, ratings of

Table 1 Selected pre-dehydration and pre-experimental testing variables for NaCl and Placebo treatments in 4 and 24°C environments

	DH + NaCl	DH + P	EU + P
Pre-dehydration initial body mass (kg)	80.0 ± 14.4	78.7 ± 13.7	79.0 ± 14.6
Pre-experimental Testing body mass (kg)	77.0 ± 13.6	75.8 ± 13.1	78.7 ± 14.2
% Body mass change (from pre-dehydration)	3.7 ± 1.3	3.7 ± 0.5	$0.4 \pm 0.9^\#$
Pre-dehydration U_{SG} (afternoon)	1.007 ± 0.005	1.005 ± 0.005	1.009 ± 0.006
Pre-experimental testing U_{SG} (morning)	1.025 ± 0.003	1.027 ± 0.003	$1.011 \pm 0.004^\#$
Pre-experimental testing P_{osm} ($\text{mOsm kg}^{-1} \text{H}_2\text{O}$)	294.9 ± 3.8	294.7 ± 2.6	$287.0 \pm 3.5^\#$
Pre-experimental testing thirst perception	6.8 ± 1.3	6.8 ± 1.5	$2.5 \pm 1.0^\#$

All data are presented as mean \pm SD

$^\#$ Significant ($P < 0.05$) difference from DH + NaCl and DH + P treatments

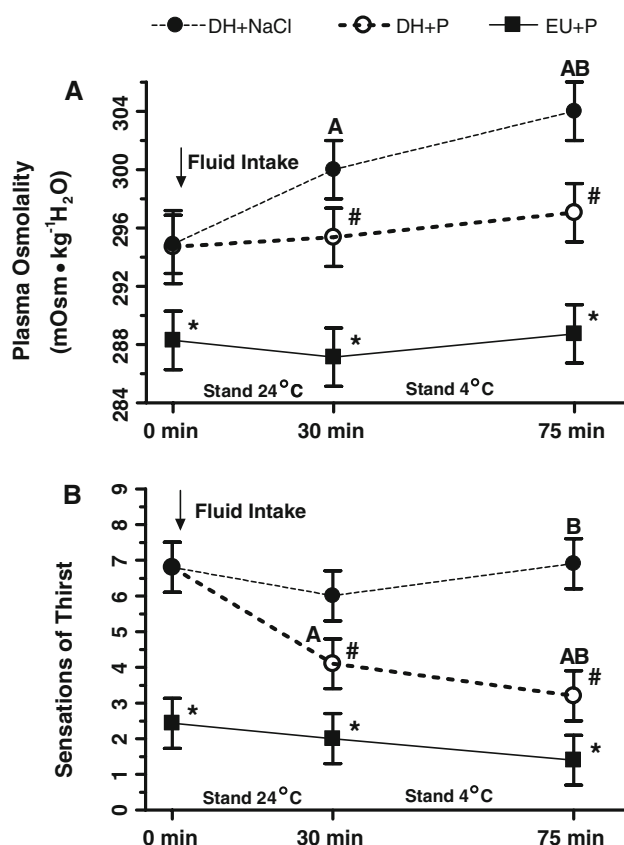


Fig. 2 Plasma osmolality (**a**) and Sensations of Thirst (**b**) versus time during DH + NaCl (filled circle), EU + P (filled square), and DH + P (open circle) trials. Asterisk denotes significant difference ($P < 0.05$) from corresponding time point in the DH + NaCl and DH + P treatments. Hash denotes significant difference ($P < 0.05$) from corresponding time point in the DH + NaCl treatment. **a** Significant difference ($P < 0.05$) from 0 min within a treatment. **b** Significant difference ($P < 0.05$) from 30 min within a treatment. All data are presented as mean \pm SD

thirst were greater ($P < 0.05$) at 0, 30 and 75 min in both of the DH treatments compared to EU + P. Thirst ratings were also greater ($P < 0.05$) in the DH + NaCl versus DH + P treatment at 30 and 75 min (Fig. 2b).

Discussion

Previous work from our laboratory showed up to a 40% decrease in thirst during rest and exercise when subjects were exposed to cold (4°C) air even when made hyperosmotic by dehydration (Kenefick et al. 2004a). We hypothesized that cold exposure caused an upward shift in the osmotically induced threshold for thirst stimulation, secondary to an increase in central blood volume induced by peripheral vasoconstriction. In the present study we set out to determine if this cold-induced thirst inhibition could be overcome by further increasing P_{osm} above that associated with DH alone. The primary findings of this study further

support thirst attenuation in the cold. In addition, these results demonstrate that this attenuation can be overridden by increasing P_{osm} . While acute dehydration in the cold has not been shown to alter cardiovascular or thermoregulatory function (Kenefick et al. 2004b) or exercise performance (Cheuvront et al. 2005), chronic voluntary dehydration has been noted as a major problem for individuals during long term exposure to cold and may increase the risk of peripheral cold injury (O'Brien et al. 1998). These results have phenomenological importance for understanding thirst regulation in cold environments and potential application in helping to drive thirst sensation and fluid intake to prevent chronic dehydration when working or exercising in the cold (Freund and Sawka 1996). Generalizability of these findings may be limited only to men as menstrual cycle-induced fluctuations in fluid status and plasma volume can independently alter the osmotic set point for thirst and the interaction of exposure to cold is unknown.

The administration of NaCl in the present study resulted in a significant elevation of P_{osm} in the DH + NaCl treatment compared to the DH + P and EU + P treatments. Ratings of thirst were also significantly greater in the DH + NaCl treatment 30 min after dosing and after 45 min of exposure to 4°C compared to the DH + P and EU + P supporting our hypothesis that the attenuation of thirst due to cold exposure can be over-ridden by elevating P_{osm} . While ratings of thirst did significantly decline in the DH + P treatment 30 min after dosing despite virtually unchanged P_{osm} , we believe that this decrease was due to the stimulation of the oropharyngeal reflex which has been shown to cause a decline in plasma arginine vasopressin as well as thirst sensations (Salata et al. 1987). While not a significant decrease, 30 min after dosing thirst declined slightly in the DH + NaCl and EU + P treatments, also likely due to drinking. A 30 min period was allowed after dosing to allow for equilibration of fluid throughout body compartments. However we did observe a continual increase in P_{osm} after 30 min in the DH + NaCl treatment either due to NaCl not entirely exiting the gut by 30 min and/or as a result of hemoconcentration associated with standing.

A change in the osmotic threshold for arginine vasopressin due to alterations in plasma volume was demonstrated in humans by Moses and Miller (1971). They reported that the osmotic threshold for plasma arginine vasopressin release was mediated by central volume changes and suggested that there may be a similar interaction between osmotic and volume stimuli for thirst. Accordingly, a decrease in plasma volume would lower the osmotic threshold, while an increase in plasma volume would elevate the osmotic threshold. Given the strong relationship between thirst and plasma arginine vasopressin (Thompson et al. 1986), it is reasonable to assume that changes in plasma

volume have the same effect on thirst. In the present study we speculate that an increase in central volume resulted in a decline in thirst sensation evidenced in the DH + P and EU + P treatments after cold exposure, despite an elevated P_{osm} in the DH + P treatment. Importantly, further elevating P_{osm} via NaCl ingestion in the DH + NaCl treatment maintained thirst, likely due to osmoreceptor stimulation. The results of this study suggest that at rest, cold exposure elevates the osmotic threshold to stimulate thirst to $\sim 304 \text{ mOsm kg}^{-1}$ of H_2O due to an increase in central volume which is greater than the reported osmotic threshold for thirst stimulation ($\sim 290 \text{ mOsm kg}^{-1}$ of H_2O) (Phillips et al. 1985).

Previously we observed a blunting of thirst along with a decrease in plasma arginine vasopressin in subjects who were hyperosmotic and hypovolemic upon exposure to cold (4°C) (Kenefick et al. 2004a). In the present study, cold exposure again resulted in an attenuation of thirst. A strong relationship has been reported between P_{osm} and thirst sensations and between P_{osm} and plasma arginine vasopressin (Phillips et al. 1985; Thompson et al. 1986). Typically as P_{osm} increases, plasma arginine vasopressin and thirst increase. This relationship has been illustrated in numerous studies (Greenleaf 1992; O'Brien et al. 1998; Phillips et al. 1985; Stricker et al. 2002; Thompson et al. 1986). However, changes in central volume have been shown to alter this relationship between thirst and P_{osm} . Stressors that increase central volume, such as head-out water immersion, have also been reported to result in a decline in drinking and thirst sensations in dehydrated subjects (Sagawa et al. 1992; Stachenfeld et al. 1997). Cold exposure has also been shown to increase central volume and alter the osmotic thirst threshold in animals. Sobocinska and Kozlowski (1987) observed dogs exposed to low ambient temperatures ($1\text{--}8^\circ\text{C}$) and reported that exposure to low ambient temperatures caused an increase in osmotic threshold for thirst as the result of a concomitant increase in central blood volume. As reported previously (Kenefick et al. 2004a), we believe that when exposed to cold, plasma arginine vasopressin and thirst sensations decline due to loading of central baroreceptors, secondary to cold-induced peripheral vasoconstriction, overriding the impact of dehydration and elevated osmolality.

Although no measures of central blood volume or central pressures were made in the present study, we have measured peripheral and central pressure (via transformation of radial artery pressure waveform) previously (Edwards et al. 2006). In that study we found an increase in central systolic pressure after 30 min of exposure to 4°C . Thus it is reasonable that in the present study, under the same conditions as Edwards et al. (2006), there was a central redistribution of blood flow. While a decrease in heart rate is typically reported when individuals are exposed to cold, caused by

an increase in central blood volume and ventricular preload, we did not observe a significant decrease in heart rate in the present study. Previously we have reported a lack of difference in heart rate in eu- and dehydrated (-4% body mass) individuals exercising in 4°C at $50\% \text{ VO}_{2\text{max}}$ (Kenefick et al. 2004b). In that study there was a significant increase in stroke volume and cardiac output when exposed to 4°C , while heart rate was not different in either eu- or dehydrated conditions.

Conclusions

Our findings support previous observations that exposure to cold attenuates thirst when dehydrated even when hyperosmotic and hypovolemic. However, the unique findings of the current study suggest that the attenuation of thirst due to cold exposure can be over-ridden by further increasing P_{osm} .

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